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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/731,971	12/08/2000	David M. Anderson	016754/0206	1748

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FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	11

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/731,971	ANDERSON ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11-22-03* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 21-72* is/are pending in the application.

4a) Of the above claim(s) *21-31 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 32, 34-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1 and 21-72 are currently pending in this application. Claims 21-31, and 33 remain withdrawn from consideration as being drawn to non-elected subject matter. Claims 1 and 32, 34-72 are now under consideration.

Applicants' amendments and arguments filed on 11-22-02, paper No.10, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claim 35 is objected to because of the following informalities: Claim 35 refers to claim 1 in plurals. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 46 recites the phrase "to anyone of claim 45". It is not clear to the Examiner as to what applicants mean by the above phrase as claim 46 appears to be dependent on only a single claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 32, 34-39, 41-49, 53, 55-61, 65-67, 69-72 are rejected under 35 U.S.C. 102(b) as being anticipated by Beudeker et al. (EP 0743017 A2, 11-20-1996). This rejection is based upon the public availability of a printed publication. Claims 1, 32, 34-39, 41-49, 53, 55-61, 65-67, 69-72 of the instant application are drawn to a composition comprising, a) an enzyme that cleaves a linkage that effects release of a cell-surface protein or carbohydrate, said enzyme being other than an endo-1,4-D-mannase, and b)a physiologically acceptable carrier for said enzyme, wherein said composition is in form suitable for oral administration, wherein said enzyme effects a release of a cell-surface protein, and having further limitations including wherein said composition contains no other anti-infection agent (claims 32 and 35), wherein said composition is a feed (claim 34), wherein said enzyme is selected from a group consisting of sphingomyelinase and phospholipases (claims 38 and 66), wherein the enzyme carrier is a food stuff (claims 45 and 56) and wherein said food stuff is an animal feed comprising grains such as sorghum, wheat etc. (claims 46, 47, 57, 58) and wherein the composition is a solid or a liquid formulation (claims 49 and 60) and wherein the enzyme is alternatively obtained by expression of recombinant DNA in a host microorganism (claim 53). Thus it appears that applicants invention comprises making compositions of animal feeds incorporated with the phospholipase enzyme derived from *B.cereus*. Beudeker et al. disclose an identical composition comprising

phospholipase. The reference is mainly drawn to an animal feed particularly plant based feeds comprising such enzyme and carriers and stabilizers required for use of the enzyme in the feed (see the entire reference). Therefore, Beudeker et al. anticipate claims 1, 32, 34-39, 41-49, 53, 55-61, 65-67, 69-72 of this application as written.

Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the composition of the prior art does not possess the same material structural and functional characteristics, i.e., the stabilizers and carriers of phospholipase of the claimed composition). See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re* Fitzgerald et al., 205 USPQ 594.

Claims 32, 56-65, 69-72 are rejected under 35 U.S.C. 102(b) as being anticipated by Fodge et al. (WO 97/41739, 13 Nov. 1997, ref. In IDS). This rejection is based upon the public availability of a printed publication. Claims 32, 56-65, 69-72 of the instant application are drawn to a composition comprising, a) an enzyme that cleaves a linkage that effects release of a cell-surface protein or carbohydrate, and b)a physiologically acceptable carrier for said enzyme, wherein said composition is in form suitable for oral administration, wherein said enzyme effects a release of a cell-surface protein, wherein said composition contains no other anti-infection agent, wherein said composition is a feed comprised of grain material, a source of protein, vitamins, amino acids and minerals, wherein the composition is in a solid form or a liquid form wherein the enzyme is contained in a tablet or gelatin capsule shell, wherein the enzyme is a

hemicellulases, a mannanase, such as endo-1,4-ß-D-mannanase produced by *B.lentus* ATCC 55045, wherein the composition further comprises a stabilizer, a carrier or preservative. Thus it appears that applicant's invention comprises compositions of animal feeds incorporated with hemicellulases such as a mannanase, such as endo-1,4-ß-D-mannanase produced by *B.lentus* ATCC 55045. Fodge et al. disclose an identical composition comprising a hemicellulase, such as a mannanase, such as endo-1,4-ß-D-mannanase produced by *B.lentus* ATCC 55045. The reference is mainly drawn to an animal feed comprising such enzyme as above. Therefore, Fodge et al. anticipate claims 32, 56-65, 69-72 of this application as written.

Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the composition of the prior art does not possess the same material structural and functional characteristics, i.e., the stabilizers and carriers of phospholipase of the claimed composition). See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re* Fitzgerald et al., 205 USPQ 594.

Examiner has withdrawn the previous rejection of claims 1 and 32 under 35 U.S.C. 102(b) as being anticipated by Kuppe et al. in view of arguments and claim amendments by applicants. However, the above new rejections have been made as it applies to amended claims and new claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 39-40, 50, 52, 54-55, 67-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beudekar et al. (EP 0743017 A2, 11-20-1996). as applied to claims 1, 32, 34-38, 41-49, 51, 53, 56-61, 65-66, 69-72 above, and further in view of Kuppe et al. (J. Bacteriol., 1989, Vol. 171(11):6077-6083) and Barbis et al. (Brazilian J. Med. Biol. Res., 1994, Vol. 27:401-407, A14 on IDS). Claims 39-40, 50, 52, 54-55, 67-68 in this instant application are drawn to a composition comprising a) an enzyme that cleaves a linkage that effects release of a cell-surface protein or carbohydrate, said enzyme being other than an endo-1,4-D-mannase, and b)a physiologically acceptable carrier for said enzyme, wherein said composition is in form suitable for oral administration, wherein said enzyme effects a release of a cell-surface protein, wherein said composition contains no other anti-infection agent, wherein said composition is a feed, wherein said enzyme is selected from a group consisting of sphingomyelinase and phospholipases which are of type C (PLC) or type D and is phosphatidylinositol-specific phospholipase C, wherein the enzyme carrier is a food stuff and wherein said food stuff is an animal feed comprising grains such as sorghum, wheat etc. and wherein the composition is a solid or a liquid formulation and wherein the enzyme is prepared from *B.cereus* strains such as ATCC 7004 or ATCC6464, wherein the enzyme is alternatively obtained by expression of recombinant DNA in a host such as B.megaterium and the enzyme is represent at 200 IU/kg to

4000 IU/kg feed. Thus it appears that applicants invention comprises compositions such as animal feeds incorporated with the phospholipase enzyme derived from *B.cereus* which takes the place of an antibiotic in order to reduce the use of antibiotics in animal feeds.

The reference of Beudeker et al. as it applies to claims 1, 32, 34-38, 41-49, 51, 53, 56-61, 65-66, 69-72 has already been discussed above. The reference of Beudeker et al. primarily teaches the use of phospholipases in animal feed compositions. However, the reference does not teach specifically the use of phosphatidylinositol-specific phospholipase C in the feed composition, specifically the enzyme isolated from *B.cereus* ATCC strains and obtained as a recombinant enzyme from the host B.megaterium strain and at the dosages of 200 IU/kg to 4000 IU/kg.

Kuppe et al. teach the purification and characterization of phospholipase C (PLC) from *B.cereus*. The reference also teaches the amino acid sequence and the polynucleotide sequence of the gene encoding the enzyme. The reference teaches the isolation of the enzyme from *B.cereus* ATCC 6464 and demonstrates that the enzyme is a phosphatidylinositol-specific PLC capable of cleaving anything linked through phosphatidylinositol linkage. The reference teaches, that in mammals the enzyme plays a key role in transmembrane signal transduction involving Ca2+ mobilizing growth factors and hormones (see introduction). However, the reference does not teach the use of the enzyme in animal feed.

Barbis et al. teach that a number of cell surface molecules (including proteins) are anchored in the cell membrane by glycosylphosphatidylinositol (GPI) and that these molecules are involved in various properties of the cell. The reference also clearly teaches that many GPI-anchored proteins on the cell membrane can be released by treatment with phosphoinositol-

specific PLC. The same reference also teaches that a variety of such GPI-anchored molecules on cell surfaces act as cellular receptors for enveloped or non-enveloped viruses. The reference further teaches canine parvo virus (CPV) binds to a protein moiety which is a GPI-anchored protein on the cell surface. The reference teaches that pretreatment of such cells with PLC removed the GPI-anchored proteins from the cell surface rendering them resistant to infection by the CPV virus. In essence, the reference teaches that PLC treatment of cells can render them resistant to virus infection.

Armed with the above three references, it would have been obvious to one of ordinary skill in the art to combine the teachings of the three references, i.e., phospholipases can be used as a part of a feed, that the purified enzyme/recombinant enzyme composition provided by Kuppe et al. can be used to fortify an animal feed such that the animal consuming such feed would be imparted with a mechanism to avoid viral infection, for example, especially those viruses that attach through the cells of the intestinal tract. The added PLC in the feed would rid the intestinal cells of the GPI anchoring proteins that would otherwise aid the viruses to infect the intestinal cells. Using the cDNA clone provided by Kuppe et al. it would also have been obvious to one of ordinary skill in the art to sub-clone the above enzyme and produce it by recombinant methods using any of the host cells including *B.megaterium* and such recombinant methods are widely known and used in the art of molecular biology. One of ordinary skill in the art would be motivated to do so as use of PLC in animal feeds would essentially provide a means to fight viral infection in animals. One of ordinary skill in the art would have a reasonable expectation of success since Beudeker et al. already show that phospholipases can be safely used as a part of animal feed, Kuppe et al. provide a purified/recombinant enzyme from

B.cereus and the reference of Barbis et al. clearly teaches the role of PLC enzyme in preventing viral infection such that PLC can be used as antiviral-like compound.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicants have traversed the above rejection arguing basically that the suggestion and the reasonable expectation of success must be founded in the prior art and not n the applicant's disclosure. Examiner does agree with the applicant regarding the above aspect of an obviousness rejection and Examiner has indeed shown that such is the case.

Applicants argue that even though Barbis et al. reference teaches that PLC severely compromises the ability of canine parvovirus to infect the cell *in vitro*, the reference does not teach the making of a PLC formulation. Applicants also point out that Barbis et al. obtained a commercial PLC and used an extremely dilute concentration and that such dilute concentrations would not be suitable for oral formulation and therefore there is not reasonable expectation that the *in vitro* showing of PLC action by Barbis would successfully work well *in vivo*. Applicants also argue that a knowledgeable reader informed by Barbis would not have been prompted to orally administer a PLC preparation for treating or lowering the risk of digestive tract infections. Examiner respectfully disagrees with applicants argument. This is because applicants are arguing that for the obviousness type of rejection, the references should teach all the limitations of the claims. However, there is no such requirement that all the references used n the rejection must teach each and every limitation of the claims, because some of the limitations may already be taught in the art or be well known in the art. Applicants argument that Barbis et al. uses a

commercial preparation, uses dilute concentrations of the enzyme, does not teach the formulation of the enzyme and provides only *in vitro* data are all misplaced. What is important in the Barbis reference are the following a) the finding that a number of cell surface molecules (including proteins) are anchored in the cell membrane by glycosylphosphatidylinositol (GPI) and b)that these molecules are involved in various properties of the cell and that many GPI-anchored proteins on the cell membrane can be released by treatment with phosphoinositol-specific PLC and c)the same reference also teaches that a variety of such GPI-anchored molecules on cell surfaces act as cellular receptors for enveloped or non-enveloped viruses and d)the reference further teaches canine parvo virus (CPV) binds to a protein moiety which is a GPI-anchored protein on the cell surface and pretreatment of such cells with PLC removes the GPI-anchored proteins from the cell surface rendering them resistant to infection by the CPV virus. In essence, the reference teaches that PLC treatment of cells can render them resistant to virus infection. The above findings even though are all based on *in vitro* experiments are crucial to prove the usefulness of PLC enzyme and applicants have not provided any specific reason as to why such data will not be useful for formulating compositions to be used *in vivo*. It is well recognized in the art that many *in vitro* experimental data can be soundly used for *in vivo* purposes (for example enzyme inhibitors isolated from *in vitro* assays are used as drugs). Combining such teachings with the reference of Kuppe et al. --in which the cDNA for such a PLC is taught-- and Beudeker et al. --which teaches the use of phospholipase in animal feeds--, it would have been *prima facie* obvious to one of ordinary skill in the art to fortify animal feeds with PLC such that it would provide a means for the animals to overcome at least lower the risk of viral infections. Aspects such as formulating a dosage, the specific dose itself and also to make the PLC as a

recombinant enzyme using a host cell such as *B.megaterium* or any such suitable host are all well within the skill of those artisans in the art. Examiner respectfully disagrees with the applicant's argument that the references of Kuppe et al. and Barbis et al. are patentability-defeating references since they both fail to disclose compositions that are physiologically acceptable for oral administration in treating and lowering the risks of digestive tract infections for the very same reasons recited above. Contrary to applicant's argument Examiner has clearly provided *prima facie* evidence which renders the above claim obvious. Therefore the above rejection is maintained.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 6:30 a.m. to 3:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1600~~ 1605

Manjunath N. Rao Ph.D.

2/6/03